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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,051	01/31/2001	Philip Jordan Thomas	UTSD:703US/SLH	3186

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EXAMINER
GUNTER, DAVID R

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/775,051

Applicant(s)

THOMAS ET AL.

Examiner

Gunter David

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 May 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. The instant application was deemed to be subject to restriction as outlined below in paragraph 2. On May 2, 2002, as a result of a telephone interview, Steven Highlander, attorney for the applicants, elected Claim Group I (Claims 1-29) and made a further election of species in regard to Claim 10 (beta-galactosidase) and Claim 13 (maltose-binding protein). The attorney did not indicate that the elections were made with traverse (Interview Summary, paper number 11, mailed May 13, 2002). Affirmation of this election must be made by applicant in replying to this Office action.

Applicant's election without traverse of Claims 1-29 is acknowledged, and all other Claims are withdrawn from consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-29, drawn to a method of assessing protein folding and/or solubility, classified in class 435, subclass 7.1.
- II. Claims 30-34, drawn to a method of screening protein folding and/or solubility, classified in class 435, subclass 6.
- III. Claims 35-40, drawn to a method of screening candidate modulator substances, classified in class 435, subclass 6.

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, invention I describes a technique for assessing the folding and/or solubility of a protein of interest. Invention II adds the step (mode of operation) of performing mutagenesis on the protein of interest. As a result, the function of the method of invention I is changed from assessing the folding and/or solubility of the wild type protein to "determining structural complementation ... as compared to the structural complementation observed with the unmutagenized fusion protein" (Specification, page 6, lines 2-5) in order to identify regions of the protein of interest involved in determining solubility.

Inventions I and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, invention I describes a technique for assessing the folding and/or solubility of a protein of interest. Invention III adds the step (mode of operation) of contacting the host cell with candidate modulator substances. As a result, the function of the method of invention I is changed from assessing the folding and/or solubility of the wild type protein to "screening [a] candidate modulator substance that modulates protein folding" (Specification, page 6, lines 7-8).

Inventions II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, invention II describes a method for identifying regions of the protein of interest involved in determining

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solubility using mutagenesis. Invention III describes a method for screening a candidate modulator substance that modulates folding of the wild-type protein of interest. Each invention has a unique mode of operation (mutagenesis for invention II and addition of a modulator substance for invention III) which results in different functions (identification of important regions within the protein of interest for invention II and identification of regulators of protein solubility in invention III).

The three inventions described above represent three distinct methods, each with a unique mode of operation, a unique function, and which each yield a distinct type of results. As a result of these differences in mode of operation, function, and effect, the literature searches required for Groups I – III would not necessarily be co-extensive, and therefore a search for more than one of these groups represents a significant burden on the examiner. Because these inventions are distinct for the reasons given above, restriction for examination purposes as indicated is proper.

This application contains claims directed to the following patentably distinct species of the claimed invention:

- a. Claim 10 recites the limitation that the marker protein is an enzyme selected from a list of eleven enzymes including beta-galactosidase.
- b. Claim 13 recites the limitation that the protein of interest is a protein selected from a list of forty proteins including maltose-binding protein.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Regarding Claim 1(a), the Claim is indefinite because the term "a gene encoding fusion protein" is unclear. The term could be read to mean that the fusion protein encodes a gene, which is not consistent with the accepted definition of "encode". The Claim should be amended to read "a gene encoding a fusion protein."

b. Regarding Claim 1(a), the Claim is indefinite because the term "in said host cell" lacks antecedent basis. The Claim includes no prior recitation of a host cell or transfection of the expression construct. The Claim should be amended to read "in a host cell."

c. Regarding Claim 1(b), the Claim is indefinite because the term "wherein said second segment is capable of structural complementation" is unclear. "Capable of" is not an active method step, and may be interpreted to recite either a property of the second segment of the marker protein or a potential method of using the second segment of the marker protein. The claim should be amended to state that the "second segment complements the structure" of the first segment.

d. Regarding Claim 1, the phrase "wherein a greater degree of structural complementation ... indicates proper folding and/or solubility of said protein" is indefinite because it is unclear whether "said protein" refers to the fusion protein, the protein of interest, or the marker protein. The claim should be amended to specifically identify the protein to which "said protein" refers.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 1-6, 16, 24, 28, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnsson and Varshavsky, Proceedings of the National Academy of Sciences of the United States of America 91:10340-4, 1994 (hereinafter referred to as "Johnsson"). Claim 1 of the instant application recites a method for assessing protein folding and/or solubility comprising: (a) providing an expression construct comprising (i) a gene encoding a fusion protein, said fusion protein comprising a protein of interest fused to a first segment of a marker protein, wherein said first segment has only systematic effects on the folding or solubility of the protein of interest, and (ii) a promoter active in a host cell and operably linked to said gene; (b) expressing said

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fusion protein in a host cell that also expresses a second segment of said marker protein, wherein said second segment complements the structure of the first segment; and (c) determining structural complementation wherein a greater degree of structural complementation, as compared to structural complementation observed with appropriate negative controls, indicates proper folding and/or solubility of said protein.

a. Regarding Claim 1, Johnsson discloses an expression construct encoding a fusion protein comprising a protein of interest (the leucine zipper homodimerization domain of *S. cerevisiae* Gcn4) fused to a first segment of a marker protein (the N-terminal portion of ubiquitin). This construct was expressed in a host cell that also expressed a second segment of the marker protein (the C-terminal portion of ubiquitin). The two segments of the marker protein complement one another to form an intact ubiquitin molecule which is recognized by cellular ubiquitinases. These ubiquitinases cleave the reconstituted ubiquitin from a signal peptide, and the amount of signal peptide liberated is measured. The degree of structural complementation is determined based on measurement of the amount of signal peptide liberated from the protein of interest and appropriate negative controls. Several negative controls that result in a partial or complete reduction in the affinity between the two segments of the marker protein by changing the folding of the fusion protein demonstrate that the degree of structural complementation is dependent on proper folding of the fusion protein (Johnsson, page 10343, both columns; also figure 4).

Johnsson discloses that an advantage of the "split ubiquitin" method over the yeast two-hybrid system is that it allows "the possibility of monitoring a protein-protein interaction as a function of time at the natural sites of this interaction in a living cell"

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(page 10343, right column, third paragraph). This lack of interference in the normal function of the protein of interest satisfies the definition of "has only systematic effects" disclosed in the specification (having "minimal impact of the fusion partners on the proteins of interest, " page 9, lines 6-7). Johnsson discloses that expression construct comprising the gene encoding the fusion protein further comprises the P_{CUP1} promoter (page 10340, right column, second paragraph). The demonstrated expression of the fusion proteins by Johnsson in figure 4 and throughout the manuscript indicates that the gene encoding the fusion protein must be "operably linked" to the gene.

- b. Regarding Claims 2 and 3, Johnsson discloses that proteins may be linked to either the C terminus or N terminus of the segments of the marker protein (page 10344, left column, first paragraph).
- c. Regarding Claims 4-6, Johnsson discloses the embodiments in which the the marker protein is ubiquitin (Claim 6). Ubiquitin satisfies the definition of "target binding protein" (Claims 4 and 5) because it specifically binds to targets within the cell including ubiquitinase.
- d. Regarding Claims 16 and 24, Johnsson discloses the embodiment in which the host cell is a yeast cell (page 10340, bottom of left column to top of right column).
- e. Regarding Claim 28, Johnsson discloses the embodiment in which the negative control utilizes a host cell lacking the second segment of the marker protein (page 10343, figure 4A and 4B, lanes a-c; also page 10343, left column).

f. Regarding Claim 29, Johnsson discloses the embodiment in which the negative control utilizes a fusion protein that is improperly folded and/or insoluble (page 10343, figure 4A and 4B, lanes j-l; also page 10343, right column).

6. Claims 1, 4, 7-9, 16-18, and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Michnick, et al., U.S. Patent Number 6,294,330, filed 7/30/1998, issued 9/25/2001 (hereinafter referred to as "Michnick"). Michnick discloses a method in which an expression construct is formed which encodes a protein of interest (GCN4 leucine zipper) fused to a first segment of a marker protein (dihydrofolate reductase). This construct is expressed in a host cell that expresses the second segment of dihydrofolate reductase, which complements the structure of the first segment to produce an active enzyme. The degree of structural complementation as determined by enzyme activity is compared to appropriate negative controls to indicate proper folding and/or solubility of the fusion protein (figure 3, panels I and II; also column 10, lines 5-37). Michnick discloses that this method will "allow for the detection of ... interactions in appropriate contexts, such as within a specific ... cellular compartment, or organelle" (column 3, lines 18-20). This lack of interference in the normal localization of the protein of interest satisfies the definition of "has only systematic effects" disclosed in the specification (having "minimal impact of the fusion partners on the proteins of interest," page 9, lines 6-7). Michnick discloses that the expression constructs comprising the gene encoding the fusion protein were subcloned into pBluescript SK+ (column 17, lines 1-2), a plasmid commercially available from Stratagene which is known in the art to contain a promoter (Stratagene online catalog, www.stratagene.com). Michnick further discloses induction of promoter activity by treatment

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transfected cells with IPTG (column 17, lines 33-35). The demonstrated expression of the fusion proteins by Michnick in figure 3 and throughout the manuscript indicates that the gene encoding the fusion protein is "operably linked" to the gene.

- a. Regarding Claim 7, Michnick discloses the embodiment in which the marker protein is a chromophore (green fluorescent protein, column 29, lines 1-24).
- b. Regarding Claim 8, Michnick discloses the embodiments in which the marker is green fluorescent protein (column 29, lines 1-24) and luciferase (column 29, lines 25-47).
- c. Regarding Claim 9, Michnick discloses the embodiment in which the marker is an enzyme (dihydrofolate reductase, column 10, lines 5-37 and luciferase, column 29, lines 25-47).
- d. Regarding Claims 16-18, Michnick discloses the embodiment in which the host cell is a bacterium (Claims 16 and 17), and the embodiment in which the bacterium is *E. coli* (Claim 18) in column 10, lines 19-36.
- e. Regarding Claim 26, Michnick discloses the embodiment in which the host cell is a mammalian cell (COS cells; column 10, line 59).

7. Claims 1, 4, 9, and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Rossi, et al., Proceedings of the National Academy of Science of the United States of America 94:8405-8410, 1997 (hereinafter referred to as "Rossi"). Rossi discloses a method in which an expression construct is formed which encodes a protein of interest (FKBP-rapamycin associated protein) fused to a first segment of a marker protein (the omega subunit of beta-galactosidase). This construct is expressed in a host cell that expresses the second segment of beta-galactosidase

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(the alpha subunit), which complements the structure of the first segment to produce an active enzyme (page 8406, right column, second paragraph). The degree of structural complementation as determined by enzyme activity is compared to appropriate negative controls to indicate proper folding and/or solubility of the fusion protein (page 8409, figure 3, panels A-D). Rossi discloses that for this method it is essential "to select [beta-galactosidase subunits] with sufficiently low affinity for each other so that they monitored rather than drove the association of the test proteins" (page 8405, right column, last paragraph through the top of page 8406, left column). This lack of interference in the normal association of the protein of interest satisfies the definition of "has only systematic effects" disclosed in the specification (having "minimal impact of the fusion partners on the proteins of interest," page 9, lines 6-7). The demonstrated expression of the fusion proteins by Rossi in figure 3 indicates that the gene encoding the fusion protein must be "operably linked" to the gene.

- a. Regarding Claims 10 and 11, Rossi discloses the embodiment in which the marker protein is beta-galactosidase (page 8406, left column, second paragraph).
- b. Regarding Claim 12, Rossi discloses the embodiment in which the first segment is the alpha peptide of beta-galactosidase and the second segment in the omega peptide of beta-galactosidase (page 8406, left column, second paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Johnsson in view of Zwick, et al., Analytical Biochemistry 264:87-97, 1998 (hereinafter referred to as "Zwick"). As described above in paragraph 5, Johnsson discloses a method in which a protein of interest is fused to one half of a marker protein, and subsequently expressed in a cell which also expresses the second half of the marker protein. Proper folding and solubility of the fusion protein results in the complementation of the two halves of the marker protein, which generates a detectable signal. Johnsson does not specifically teach that the protein of interest is maltose binding protein (MBP).

MBP was known to those of skill in the art at the time the application was filed to be a protein to which proteins of interest could be fused. Fusion of a protein of interest to MBP was known to improve the solubility of the protein (Zwick, page 88, left column, second paragraph), and antibodies specific for MBP were commercially available and known to be useful for detection or purification of maltose binding protein. Zwick further teaches a method in which

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the genes encoding proteins of interest expressed in a phage display system are subcloned to form an MBP fusion protein using commercially available vectors. Zwick teaches two advantages to creating an MBP fusion protein from the protein of interest identified in a phage display system. First, the MBP provides an antigen to which anti-MBP antibodies can bind. Second, it eliminates "potential phage effects" including "conformational effects" which may result from the presence of viral protein sequences found in the phage display vector. The phage coat proteins normally encoded by phage display vectors can alter the characteristics of the protein of interest by altering its conformation. Removal of the DNA encoding these phage coat proteins promotes normal folding of the protein of interest (Zwick, page 87, right column through page 88, left column).

It would have been obvious to one of ordinary skill in the art at the time the application was filed to assay the conformation of the MBP fusion proteins described above to insure that no residual viral sequences have altered the conformation of the protein of interest. The use of wild-type MBP would serve as an obvious control in such an assay. It would have further been obvious to use the method of Johnsson as an assay for MBP and MBP fusion proteins because of its demonstrated success, its ability to assess conformation of MBP and MBP fusion proteins regardless of their cellular localization, and its adaptability to a broad range of endpoints including assays for beta-galactosidase or luciferase activity (Johnsson, page 10343, both columns; also figure 4).

10. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnsson in view of Farzaneh, et al. Nucleic Acids Research 16(23):11319-11325, 1988

(hereinafter referred to as "Farzaneh"). As described above in paragraph 5, Johnsson discloses a method in which a protein of interest is fused to one half of a marker protein, and subsequently expressed in a cell which also expresses the second half of the marker protein. Proper folding and solubility of the fusion protein results in the complementation of the two halves of the marker protein, which generates a detectable signal. Johnsson does not specifically teach that the gene encoding the second segment is carried on the chromosome of the host cell (Claim 14) or carried episomally in the host cell (Claim 15).

It was well known in the art at the time the application was filed that foreign nucleic acids transfected into cells could either be incorporated into the genome of the host cell or carried episomally as extra-chromosomal DNA fragments. It was further known that transfected DNA is always initially episomal until recombination events within the nucleus of the cell cause it to become integrated (Farzaneh, page 11319, abstract). In addition, it was known that foreign DNA can be expressed by cells resulting in the formation of the desired protein regardless of whether the DNA is episomal or integrated into the genome (Farzaneh, page 11319, last paragraph). Therefore, it would have been obvious to one of ordinary skill in the art at the time the application was filed that the DNA encoding the marker proteins as described by Johnsson could either exist as an episomal DNA fragment or become integrated into the host genome without altering the mode of operation or end results of the assay.

11. Claims 19, 25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnsson. As described above in paragraph 5, Johnsson discloses a method in which a protein of interest is fused to one half of a marker protein, and subsequently expressed in a cell which also

expresses the second half of the marker protein. Proper folding and solubility of the fusion protein results in the complementation of the two halves of the marker protein, which generates a detectable signal. Johnsson does not specifically teach that the promoter used to drive expression of the transfected DNA is the *Taq* promoter, T7 promoter, *P_{lac}* promoter (all found in Claim 19), CupADH, Gal (both in Claim 25), PepCk, or tk (both in Claim 27). However, the examiner notes that all of these promoters were well known in the art at the time the application was filed. It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method disclosed by Johnsson to incorporate a promoter of Claims 19, 25, or 27, based on their known ability to drive expression of exogenous genes in a variety of relevant cell types and the ready availability of vectors containing these promoters.

12. Claims 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnsson. As described above in paragraph 5, Johnsson discloses a method in which a protein of interest is fused to one half of a marker protein, and subsequently expressed in a cell which also expresses the second half of the marker protein. Proper folding and solubility of the fusion protein results in the complementation of the two halves of the marker protein, which generates a detectable signal. Johnsson does not specifically teach that the host cell into which the constructs are transfected is a nematode cell (Claim 20), a *C. elegans* cell (Claim 21), an insect cell (Claim 22), or an *S. fugeia* cell (Claim 23). However, the examiner notes that all of the cell types recited in Claims 20-23 were well known in the art to be readily transfected and to express foreign DNA at high levels. Therefore, it would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Johnsson to include any of the cell types of

Claims 20-23 wherein absent unexpected results the selection of cell type would have been based on e.g. preference, available materials, and desired experimental results in order to allow assessment of protein folding in a plurality of eukaryotic hosts.

Conclusion

13. No claims are allowed.

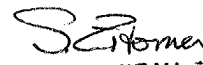
Any inquiry concerning this communication or earlier communications from the examiner should be directed to David R. Gunter whose telephone number is (703) 308-1701. The examiner can normally be reached on 9:00 - 5:00 M - F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-9212 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.



David R. Gunter, DVM, PhD
September 12, 2002



STEPHANIE W. ZITOMER
PRIMARY EXAMINER